Regarding the Information Disclosure Statement

The Office Action, at page 3, indicates that the Information Disclosure Statement filed January 19, 2001, fails to comply with the provisions of the Manual for Patent Examining Procedure because references 60-1000 lack indication of author and date on the Form 1449. Applicants will prepare and file a revised Form 1449 with the requested information for references 60-100, which refer to Genbank Accession Numbers, as a supplemental response.

Rejections under 35 U.S.C. § 112, First Paragraph

The objection to the specification and corresponding rejection of claims 12 and 13 under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification so as to enable one skilled in the art to practice the claimed invention is respectfully traversed.

The Office alleges, at page 4, first paragraph, of the Action mailed November 5, 2002 (Paper No. 13), that the specification does not reasonably provide enablement for a method of determining the efficacy of a compound in ameliorating a vigilance disorder in individuals that may include mammals or humans. For the reasons that follow, Applicants respectfully submit that the specification provides teachings and guidance to sufficiently enable the full scope of claims 12 and 13.

Applicants respectfully disagree with the assertion that defining and narrowing of the vigilance disorder is a prerequisite for enablement of the rejected claims, which disclose and enable a broader invention. Applicants direct the Examiner's attention to the specification, which teaches that a vigilance disorder encompasses any condition that disturbs the normal sleep and wake patterns of an individual (specification, page 62, lines 5-7). The specification further discloses that a vigilance disorder can have a genetic or familial basis; can have a psychiatric or medical basis; can be induced by substances including medications and drugs; or can have any combination of these underlying causes (specification, page 62, lines 7-11). Also disclosed are exemplary vigilance disorders including various forms of insomnia, hypersomnia, narcolepsy, parasomnias, sleepwalking disorder, sleep apnea, restless legs syndrome (RLS) and fatal familial insomnia (specification, page 62, lines 11-15). Further with regard to a vigilance disorder, the specification indicates that variety of vigilance disorders in humans are described in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (1994), published by the American Psychiatric Association (specification, page 62, lines 15-18). Given this guidance, the skilled person would have been able to identify and select a vigilance disorder useful for practicing the methods of the invention.

Applicants also disagree with the assertion that association of a vigilance disorder with a particular gene expression profile is a prerequisite for enablement of the rejected claims. As set forth above, the specification provides guidance to the skilled

person with regard to what constitutes a vigilance disorder useful for practicing the methods of the invention. With regard to enablement of the vigilance gene profile of the individual, the specification also provides detailed teachings and guidance to the skilled person that allow for establishing a vigilance gene profile without undue experimentation.

The specification teaches that a vigilance gene profile refers to any read-out that provides a qualitative or quantitative indication of the expression or activity of a single vigilance gene, or of multiple vigilance genes (specification, page 65, lines 17-20). As further guidance to the skilled person, the specification teaches that a vigilance gene profile can, for example, indicate the expression or activity of one, or of least 2, 5, 10, 20, 50, 100 or more vigilance and also can, for example, indicate the expression or activity in mammals of mammalian homologs of one or more vigilance genes identified as such from the invertebrate screening assays described in the specification, such as *Fas, BiP, Cyp4e2, AANAT1 (Dat), Ddc*, or a gene containing any of SEQ ID NOS:2-6 (specification, page 65, lines 20-28). In this regard, claims 12 and 13 recite and the specification teaches that at least one of the vigilance genes profiled is selected from the group consisting of *Fas, BiP, Cyp4e2, AANAT1 (Dat), Ddc, Cytochrome P450*, AA117313, *aryl sulfotransferase IV*, human breast tumor autoantigen homolog, KIAA313 homolog, *E25*, and a gene containing SEQ ID NOS:2-6, 8-14, or 16-27 or modification thereof (specification, page 65, line 28 to page 66, line 4).

As further guidance to the skilled person the specification discloses that a vigilance gene profile can indicate the expression or activity of one or more vigilance genes identified as such from published mammalian studies described above, including *NGFI-A, NGFI-B,* rlf, *Arc, JunB, IER5, Cytochrome oxidase C subunit 1, Cytochrome oxidase C subunit IV, NADH dehydrogenase subunit 2, 12S rRNA F1-ATPase subunit alpha,* Ng/RC3, bone morphogenetic protein 2, GRP78, BDNF, IL-1β, dendrin, Ca^{++}/calmodulin-dependent protein kinase II α-subunit, orexin, orexin receptor, and PRNP (specification, page 66, lines 4-13).

Further enablement regarding a vigilance gene profile is provided by the teaching that the profile can be, for example, a quantitative or qualitative measure of expression of mRNA expressed by a vigilance gene (specification, page 66, lines 21-23). In this regard, the specification dislcoses a variety of routine methods of detecting or quantitating mRNA expression that have been described in connection with invertebrate screening assays and include, without limitation, Northern or dot blot analysis, primer extension, RNase protection assays, differential display, reverse-transcription PCR, competitive PCR, real-time quantitative PCR (TaqMan PCR), and nucleic acid array analysis (specification, page 66, lines 23-30).

Additional enablement regarding a vigilance gene profile is provided by the teaching that the profile can be, for example, a quantitative or qualitative measure of expression of polypeptides encoded by vigilance genes (specification, page 67, lines 1-4).

In this regard, the specification discloses a variety of routine methods of detecting or quantitating protein expression have been described in connection with invertebrate screening assays, and include, but are not limited to, immunohistochemistry, immunofluorescence, immunoprecipitation, immunoblot analysis, and various types of ELISA analysis, including ELISA analysis using arrays of vigilance-polypeptide specific antibodies bound to solid supports, as well as additional methods including two-dimensional gel electrophoresis, MALDI-TOF mass spectrometry, and ProteinChip™/SELDI mass spectrometry technology (specification, page 67, lines 4-13).

The specification further teaches that a vigilance gene profile a direct or indirect measure of the biological activity of polypeptides encoded by vigilance genes (specification, page 67, lines 14-16). As further guidance, the specificaton teaches direct measures of the biological activity of a vigilance polypeptide, including, measures of enzymatic activity,as well as indirect measures such as the polypeptide's state of modification (e.g. phosphorylation or glycosylation), localization (e.g. nuclear or cytoplasmic), abundance of a substrate or metabolite of the polypeptide, such as a neurotransmitter (specification, page 67, lines 16-29). The specification also teaches that a vigilance gene profile can be established *in vivo*, such as by diagnostic imaging procedures using detectably labeled antibodies or other binding molecules, or from a sample obtained from an individual that can contain, for example, neural tissue, cells derived from neural tissues, or extracellular medium surrounding neural tissues, in which vigilance polypeptides or their

metabolites are present such as human cerebrospinal fluid (specification, page 68, lines 14-27).

Further with regard to enablement of a vigilance gene profile, the specification teaches that the vigilance gene(s) to be profiled can be determined by those skilled in the art, depending on the type of vigilance-altering compound it is desired to identify or characterize (specification, page 72, lines 8-11). It is further taught that an expression or activity profile of one or many vigilance genes can be established that is a molecular fingerprint of each mammalian vigilance level, state or disorder of interest and, further, that, in screening applications, identification of vigilance genes and their role in vigilance allows novel vigilance-altering compounds to be identified, lead compounds to be validated, and the molecular effects of these compounds and other known vigilance-altering compounds to be characterized, by determining the effect of these compounds on a vigilance gene profile (specification, page 44, lines 18-27).

The specification further teaches that it may be advantageous to examine the effect of a compound primarily on single genes whose causative role in vigilance has been established, including *Dat*, *Ddc*, orexin, orexin receptor and PRNP; or only or primarily on those vigilance genes whose expression or activity is upregulated during sleep; or only or primarily on those vigilance genes whose expression or activity is upregulated during wake; or only or primarily on those genes whose expression is modulated during sleep rebound, during

sleep-wake transition, or in the period following restorative or disrupted sleep (specification, page 72, lines 8-21). The specification also teaches that a additional vigilance genes can be identified by a variety of methods in addition to the exemplified methods, including differential display, arrays, and other forms of expression or activity analysis in invertebrates and mammals; genetic methods, such as by randomly or specifically targeting genes in model organisms such as *Drosophila* or mouse, or by mapping genes associated with vigilance disorders or altered vigilance properties; or from screens for genes associated with other behaviors or molecular pathways that are subsequently determined to be associated with vigilance (specification, page 73, lines 16-26).

Given the detailed guidance and teachings provided by the specification, the skilled person would have been able to select a vigilance disorder and establish a corresponding vigilance gene profile via routine methods known in the art and not requiring undue experimentation. Furthermore, armed with these teachings the skilled person would have been able to practice the claimed methods of determining the efficacy of a compound in ameliorating a vigilance disorder and modulating vigilance without undue experimentation. Accordingly, Applicants respectfully request removal of the rejection of claims 12 and 13 under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification so as to enable one skilled in the art to practice the claimed invention.

Rejections under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 12 and 13 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, respectfully is traversed. Applicants submit that the terms cited by the Examiner as indefinite is clear and definite in view of the specification for the reasons which follow.

The Federal Circuit has had the opportunity to decide a number of § 112, second paragraph issues. It is clear from these decisions that definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See, e.g., *In re Marosi*, 710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983); *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 221 U.S.P.Q. 1 (Fed. Cir. 1984); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983); and *Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 53 U.S.P.Q.2d 1225 (Fed. Cir. 1999) (district court failed to consider the knowledge of one skilled in the art when interpreting the patent disclosure).

As part of the allegation that claims 12 and 13 are indefinite, the Examiner alleges that "behavioral disorders are

very complicated, and involve numerous genes" (current Office Action, page 6, last paragraph). Applicants respectfully submit that the skilled person is charged with knowledge of the nature of vigilance disorders and, given the content of the disclosure, would have understood the metes and bounds of Applicants' claimed invention.

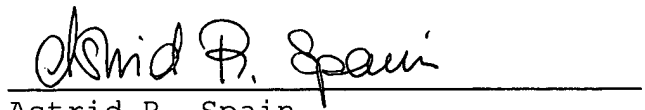
With regard to the clarity and particularity with which the claim terms are defined, the specification, at page 43, lines 21-26, clearly defines "vigilance genes" as genes that are either vigilance-modulated or vigilance-altering. The specification defines a vigilance disorder as any condition that disturbs the normal sleep and wake patterns of an individual (specification, page 62, lines 5-7). The specification further discloses that a vigilance disorder can have a genetic or familial basis; can have a psychiatric or medical basis; can be induced by substances including medications and drugs; or can have any combination of these underlying causes (specification, page 62, lines 7-11). Also disclosed are exemplary vigilance disorders including various forms of insomnia, hypersomnia, narcolepsy, parasomnias, sleepwalking disorder, sleep apnea, restless legs syndrome (RLS) and fatal familial insomnia (specification, page 62, lines 11-15). Further with regard to a vigilance disorder, the specification indicates that variety of vigilance disorders in humans are described in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (1994), published by the American Psychiatric Association (specification, page 62, lines 15-18).

Given that definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time of the invention, Applicants submit that the person of ordinary skill would have considered claims 12 and 13 as clear and definite at the time of filing. Accordingly, Applicants respectfully request removal of the rejection of claims 12 and 13 under 35 U.S.C. § 112, second paragraph, as as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

CONCLUSION

In light of the Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney or Cathryn Campbell if there are any questions related to this application.

Respectfully submitted,



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